Rejections Under 35 U.S.C. §102(e) over U.S. Patent No. 6,482,803 B1 (Roth)

The Examiner rejected claims 12-14, 18-22, 26, 30, 34-38, 42-43, and 45 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,482,803 B1 (Roth). Applicants respectfully traverse the rejection to the extent it is maintained over the claims as amended.

Anticipation under 35 U.S.C. §102 requires that all of the elements and limitations of the claim(s) at issue be found within a single prior art reference. *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

Roth does not teach all the elements and limitations of Applicants' claims. The differences between the Roth reference and Applicants' claimed invention are discussed below.

Applicants' claimed methods, compositions, and kits are directed at targeting coding sequence of RNAs with suppression effectors and providing a replacement nucleic acid to which the suppression effector cannot bind and/or cleave because the "wobble" or third nucleotide or base in at least one codon of the replacement nucleic acid has been altered. Because the third base in a codon is degenerate, it can be changed appropriately so that the amino acid that the codon encodes does not change and thus the protein the replacement nucleic acid encodes is not affected, e.g., it is wild-type or otherwise non-disease causing. This allows for the simultaneous knock-out of a deleterious RNA by the suppression effector and replacement of the deleterious RNA with a nucleic acid that encodes a wild-type or non-disease causing allele that is not suppressed, or is only partially suppressed, by the suppression effector. In addition, Applicants' claimed suppression effectors bind to and suppress mature RNAs.

Roth reports a ribozyme that targets only intron/exon splice junctions of the p53 pre-mRNA. Roth does not disclose or suggest a ribozyme, or any other molecule, that targets coding sequences in RNAs. In addition, Roth's ribozymes and methods cannot target mature RNAs.

In fact, Roth teaches away from Applicants' claimed invention. In column 3, lines 1-16, Roth states:

> This invention generally relates to expression constructs that express a ribozyme that inactivates pre-mRNA of the mutant p53 and methods for their use . . . This invention also relates to the design of ribozymes that will interrupt the pre-mRNA splicing process of p53 transcripts. An advantage of this method for modifying pre-mRNA is that joint sequences between introns and exons can be used to develop ribozyme target sequences. Such a ribozyme cleaves the target sequence and interrupts the process of splicing from pre-mRNA to mRNA. At the same time, the ribozyme would not affect a cDNA provided to the same cell.

Thus, by requiring that a ribozyme not affect a cDNA, Roth does not contemplate use of a suppression effector that targets mature RNA or coding sequence, which is present in cDNAs. This is because Roth does not contemplate that a cDNA replacement nucleic acid can be generated according to Applicants' invention that is not suppressed by the suppression effector, because the cDNA sequences vary from the mutant allele by having at least one altered wobble base.

Roth does not identically disclose each and every element of Applicants' claims and therefore is not a proper reference under 35 U.S.C. §102. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §102(e) over U.S. Patent No. 6,025,127 (Sidransky)

The Examiner rejected claims 12-14, 16-22, 25-26, 30-38, and 42-45 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,025,127 (Sidransky).

Sidransky reports methods for detecting a number of p53 mutations in tissue samples and suppression by antisense nucleic acid or ribozyme molecules that target p53 mutations. Sidransky does not disclose replacement nucleic acids that have at least one altered wobble base in at least one codon to avoid targeting and binding of the replacement nucleic acid by a suppression effector. Although Sidransky makes a general suggestion that suppression of certain mutant p53 genes may be accompanied by

replacement therapy, Sidransky does not provide any guidance as to the nature of such a replacement gene or how a replacement gene would avoid being suppressed by an antisense nucleic acid, ribozyme, or other suppression effector. Even if, as the Examiner alleges on page 5 of the Office Action, Sidransky discloses p53 mutation targets that comprise a single nucleotide change in a wobble position of a codon compared to a wild-type p53 sequence, Sidransky does not disclose, or provide a motivation to create, a replacement nucleic acid that has at least one altered wobble base.

Sidransky therefore does not identically disclose each and every element of Applicants' claims and therefore is not a proper reference under 35 U.S.C. §102(e). Applicants respectfully request that the rejection be reconsidered and withdrawn.

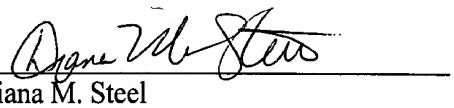
Rejections Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 12, 15, 21-22, 25-26, 28, 31, 37-38, and 41-44 under 35 U.S.C. §112, first paragraph. Not in acquiescence of the rejection but in order to expedite prosecution and allowance of the claims, Applicants have canceled claims 15 and 31, thereby rendering the rejection moot. This amendment is made without prejudice to the filing of a continuation application to pursue those claims in other related co-pending cases.

CONCLUSION

Applicants respectfully urge that all claims are in condition for allowance and request prompt and favorable action on the instant application.

Respectfully submitted,



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Marked-Up Version of the Amended Claim

12. (Amended) A method for [designing] preparing a suppression effector and replacement nucleic acid, said method comprising:

a) [determining at least a portion of a nucleotide sequence of a mutant allele;

b) designing] preparing a suppression effector that binds to a coding region of a mature RNA encoding a mutant allele [said portion], thereby to inhibit the expression of the mutant allele; and

[c) designing] b) preparing a replacement nucleic acid that encodes a wild-type or non-disease causing allele and that [which varies from the mutant allele by having one or more] comprises at least one degenerate / wobble [sites] nucleotide that [are] is altered so that the replacement nucleic acid is not [inhibited] suppressed, or is only partially suppressed, by the suppression effector[, wherein the replacement nucleic acid encodes a wild-type or non-disease causing protein].

13. (Amended) A method for [designing] preparing a suppression effector and replacement nucleic acid, the method comprising:

a) [determining at least a portion of a nucleotide sequence of a mutant allele;

b) identifying the presence of a ribozyme cleavage site on the mutant allele;

c) designing] preparing a ribozyme that cleaves [an RNA encoded by the] a mature RNA encoding a mutant allele of; and

[d) designing] b) preparing a replacement nucleic acid [which is not suppressed or is only partially suppressed, wherein the replacement nucleic acid differs from the mutant allele in] that encodes a wild-type or non-disease causing allele and that comprises at least one degenerate / wobble [position of at least one codon and wherein the replacement nucleic acid encodes a wild-type or non-disease causing protein] nucleotide that is altered so that the replacement nucleic acid is not suppressed, or is only partially suppressed, by the ribozyme.

17. (Amended) The method of claim 12, wherein the suppression effector is an [antisense] nucleic acid.

19. (Amended) The method of claim 12[or 13], wherein the suppression effector is a ribozyme [which] that cleaves an RNA encoded by the mutant allele.

20. (Amended) The method of claim 19, wherein the ribozyme cleaves [an] the RNA [encoded by the mutant allele] at an NUX ribozyme cleavage site.

27. (Amended) The method of claim 21 [or 26], wherein the expression vector is a viral expression vector.

33. (Amended) The kit of claim 44, wherein the suppression effector is an [antisense] nucleic acid.

35. (Amended) The kit of claim 44, wherein the suppression effector is a ribozyme [which] that cleaves an RNA encoded by the mutant allele.

36. (Amended) The kit of claim 35, wherein the ribozyme cleaves [an] the RNA [encoded by the mutant allele] at an NUX ribozyme cleavage site.

37. (Amended) The kit of claim 44 [or 45], wherein the suppression effector is operatively linked to an expression vector.

44. (Amended) A kit comprising:

a suppression effector that suppresses the expression of a mature RNA encoding a mutant allele; and

a replacement nucleic acid [which] that encodes a wild-type or non-disease causing allele that is not suppressed, or is only partially suppressed, by the suppression effector and that differs from the mutant allele in at least one degenerate / wobble [position] nucleotide [of at least one codon and wherein the replacement nucleic acid encodes a wild-type or non-disease causing protein].

45. (Amended) A kit comprising:

at least one ribozyme that cleaves [an RNA encoded by the] a mature RNA encoding a mutant allele; and

a replacement nucleic acid [which] that encodes a wild-type or non-disease causing allele and that is not suppressed, or is only partially suppressed, by the suppression effector, wherein the replacement nucleic acid differs from the mutant allele

in at least one degenerate / wobble [position] nucleotide [of at least one codon and wherein the replacement nucleic acid encodes a wild-type or non-disease causing protein].